SUMMARY MINUTES

MEETING OF THE NEUROLOGICAL DEVICES ADVISORY PANEL

OPEN SESSION

June 17, 2005

Hilton Washington D.C. North / Gaithersburg
Gaithersburg, Maryland

Neurological Devices Advisory Panel Meeting
June 17, 2005

Attendees

Chairperson
Stephen J. Haines, M.D.
University of Minnesota Medical School

Voting Members
Thomas J. Brott, M.D.
Mayo School of Medicine

Jonas H. Ellenberg, Ph.D.
University of Pennsylvania School of Medicine

Annapurni Jayam-Trouth, M.D.
Howard University Hospital

Mary E. (Lee) Jensen, M.D.
University of Virginia Health System

Industry Representative
Robert J. Coffey, M.D.
Medtronic, Inc.

Consumer Representative
Lee Lee Doyle, Ph.D.
University of Arkansas for Medical Sciences College of Medicine

Deputized Voting Members
Reese H. Clark, M.D.
Pediatrix Medical Group, Inc.

Mark L. Hudak, M.D.
University of Florida College of Medicine

Robert M. Nelson, M.D., Ph.D.
University of Pennsylvania School of Medicine

Food and Drug Administration
Miriam C. Provost, Ph.D., Acting Director
Division of General, Restorative and Neurological Devices

Janet L. Scudiero, M.S.
Executive Secretary

Susan S. Altaie, Ph.D.
Scientific Policy Advisor
Office of In Vitro Diagnostic Device Evaluation and Safety

Kristen A. Bowsher, Ph.D.
Lead Reviewer

Jianxiong (George) Chu, Ph.D.
Statistician

Susan N. Gardner, Ph.D.
Director, Office of Surveillance and Biometrics

Susan K. McCune, M.D., M.A.Ed.
Neonatologist-Pediatrician, Office of Pediatric Drug Development

Theodore R. Stevens, M.S.
Chief, Restorative Devices Branch

CALL TO ORDER

Panel Secretary Janet L. Scudiero, M.S., called the meeting to order at 8:30 a.m. She read the statements which appointed Reese M. Clark, M.D., Mark L. Hudak, M.D., and Robert M. Nelson, M.D., Ph.D. as temporary voting members of the Panel for the meeting. She then read the conflict of interest statement which granted a waiver to Dr. Lee Lee Doyle for her employer's interest in the sponsor's study. It was noted that the Agency took into consideration certain matters regarding Drs. Clark and Stephen Haines for their former and current (respectively) institutions' involvement with a firm at issue and determined that they may participate fully in the deliberations.

Panel Chairperson Stephen J. Haines, M.D., introduced himself and the topic of discussion for the meeting, which was the Premarket Approval Application P040025 for the Olympic Medical Corporation, Cool-Cap®, a device intended for use in infants 36 weeks gestation or older at risk for moderate to severe hypoxic ischemic encephalopathy (HIE) to provide selective head cooling with mild systemic hypothermia to prevent or reduce the severity of HIE. He then asked for introductions to be made around the table and noted that the voting members present constituted a quorum.

The agenda began with three short presentations from the FDA. **Sousan S. Altaie, Ph.D.**, the Center for Devices and Radiological Health's Critical Path Liaison gave an overview of the Agency's Critical Path Initiative and how it relates to the CDRH in particular. This initiative is FDA's attempt to make less costly and more predictable the process of getting a medical product from the design through the approval stages by modernizing the methods and techniques that assess safety, determine efficacy, and assure quality and consistency in manufacturing. She gave examples of several collaborative efforts currently underway with Stanford University, Johns Hopkins University, NIH and the CDC and encouraged attendees to provide comments to the Agency about areas of interest that could benefit from this approach and about tools that could expedite the approval of new medical technologies.

Susan Gardner, Ph.D., Director, Office of Surveillance and Biometrics (OSB), then announced a programmatic change at CDRH that transferred the condition of approval (CoA) program from the Office of Device Evaluation, to her office, OSB, which is responsible for postmarket activities. The impetus for this change was an internal evaluation that revealed that CDRH had limited and non-standardized procedures for tracking the progress and results of the condition of approval studies. This discovery prompted CDRH to 1) develop an automated system to track receipt of CoA reports, 2) add an epidemiologist to PMA review teams to consider postmarket issues early in the process, and 3) report CoA study status on the CDRH web site. Also, Panel members will be asked to consider postmarket questions during the approval process and will be updated regularly on the status of ongoing CoA studies. Dr. Ellenberg questioned FDA's regulatory authority to mandate CoA studies and impose penalties if they were not undertaken. Dr. Gardner clarified that while General Counsel was still reviewing the particulars for CoA studies, a different regulation, Section 522, provides authority for FDA regulation of postmarket studies when there is a risk to public health and the clinical

question is well formulated.

Theodore R. Stevens, M.S., Chief of the Restorative Devices Branch, provided an update on the review status of several products that had come before the Panel in the past. The Cyberonics Vagus Nerve Stimulator for Depression remains under review since the Panel made its recommendation last June. The Confluent Surgical DuraSeal Dural Sealant was approved on April 7, 2005, for adjunctive use in sutured dural repair to provide a watertight closure during cranial surgery, with a post-approval study to further evaluate complications, such as infection and CSF leak. The CoAxia NeuroFlo Catheter was approved on March 30, 2005, under the Humanitarian Device Exemption regulation for treatment of cerebral ischemia resulting from symptomatic vasospasm in patients who have not responded to other forms of treatment.

Additionally, Mr. Stevens mentioned that vascular and neurovascular embolization devices are now reclassified into class II and are reviewed under 510(k) premarket notifications provisions and that human dura mater is now considered a banked human tissue, not a medical device. The Agency also published a special controls guidance for the vascular and neurovascular embolization devices and a public health notification on MRI-caused injuries in patients with spinal cord, or other neurological implanted stimulators.

OPEN PUBLIC HEARING

Three parties requested to speak prior to the meeting. Ms. Scudiero read the open public hearing statement which encourages speakers to advise the Panel of any financial relationship they may have with the sponsor, its products, or its direct competitors. The Rosa-Davies family of Michigan, the Ottens family of Texas and the Colaizzi and Mitchell families of Michigan all had their travel expenses paid for by Olympic Medical. They testified that their children, who all suffered trauma at birth, were enrolled in the Olympic Cool-Cap® trial soon after birth. They did not suffer any significant adverse outcomes, namely death or severe neurological damage, such as seen in cerebral palsy.

SPONSOR PRESENTATION

Edward (Ted) B. Weiler, Ph.D., Vice President, Research and Development, Olympic Medical Corporation, introduced the sponsor's presenters and provided background on his company; on hyperthermia as neuroprotective therapy; and on the randomized, controlled trial for the Olympic Cool-Cap® that was the basis for the PMA submission.

Ping-Yu (PY) Liu, Ph.D. of the Fred Hutchinson Cancer Research Center was the statistician for the Cool-Cap® trial. He discussed the clinical trial design, subject enrollment, and safety and efficacy results. The Cool-Cap® trial was an international, multi-center, prospective, randomized study, with the 19 U.S. sites accounting for 75 percent of the enrollment. The efficacy objective was to evaluate whether treatment of moderate or severe HIE in term infants with head cooling and mild systemic hypothermia could produce meaningful improvements in neurodevelopmental outcome and survival rates at 18 months of age, and to confirm the safety of this treatment approach in term infants with moderate to severe HIE. The protocol called for infants to be randomized within six hours of birth to receive either 72 hours of head cooling plus mild systemic hypothermia with a goal rectal temperature of 34.5 degrees C

(plus or minus 0.5 degrees) or 72 hours of non-cooling with a target temperature of 37 degrees C (plus or minus 0.5 degrees). At hour 72, re-warming at about a half a degree centigrade per hour for four hours was begun. A total of 112 infants were cooled and 122 were not cooled.

A six-month follow-up visit was scheduled primarily to maintain contact with the family for subject retention. The primary study outcome was measured at the 18-month evaluation, where subjects underwent a neurodevelopmental examination using the Gross Motor Function (GMF) instrument, testing for mental and psychomotor disability using the Bayley Mental Development Index (MDI), and ophthalmologic and auditory assessments.

As for the safety analysis, Dr. Liu noted that there were no major cardiac arrhythmias, two cases of major venous thrombosis in the control group, three cases of severe hypotension in each group, and one death from an unanticipated skin damage adverse event in the Cool-Cap® group. Overall, there were no statistically significant differences among the anticipated serious adverse events between the cooled infants and the control group. There were three statistically significant findings among other anticipated adverse events, namely that elevated liver enzymes were actually improved in the cooled group, minor cardiac arrhythmia occurred in nine percent of the cooled group and one percent of the control group, and scalp edema was reported in 21 percent of the cooled group versus one percent of the control. The cardiac arrhythmias were mainly mild to moderate sinus bradycardia, which is expected for hypothermia, while most of the scalp edema cases were of mild to moderate severity and resolved after cooling was stopped.

As for the efficacy endpoint of mortality, among those infants whose status was known, the death rate was 31 percent in the cooled infants and 36 percent among the control, a difference that is not statistically significant.

The other efficacy endpoint, severe neurodevelopmental disability, was defined as either a Bayley MDI score of less than 70, a GMF impairment level of between 3 and 5, or bilateral cortical visual impairment. Since more infants with severely abnormal aEEG backgrounds or low Apgar scores were randomized to cooling, a pre-specified, six-factor logistic regression was performed to adjust for the chance baseline imbalances, with the result being a statistically significant treatment effect; namely, a p-value of 0.042 and an odds ratio of 0.53. Finally, Dr. Liu presented the results of some supporting analyses for the primary outcome and the results of the secondary outcomes.

John S. Wyatt, MBChB, Professor of Neonatal Pediatrics, University College London and Cool-Cap® Co-Principal Investigator, reviewed the clinical background and the logistical issues surrounding the need for early identification and referral of newborns who might be eligible for the trial, the complexities of conducting the informed consent process with distraught parents, and the challenge of achieving high rates of outcome data at 18 months follow-up in 25 hospitals around the world.

The design of the trial was based on 50 years of animal evidence which suggests that mild hypothermia after hypoxic ischemia reduces brain cell death, preserves brain energy metabolism, and ameliorates the secondary energy failure which occurs in a period between about 12 and 36-48 hours after the insult. Newborn piglet studies using the Cool-Cap® device have demonstrated that it is possible to establish a temperature gradient across the brain itself, from superficial to deep structures.

Dr. Wyatt reiterated the results of the Cool-Cap® trial from a clinical perspective, expanding on Dr. Liu's safety analysis and highlighting the trend to reduced mortality in the cooled group, although the difference was not statistically different. He offered an explanation

for the increase in mortality in the cooled group at Days 4 and 5, which was that for infants obviously doing poorly, this represents the time following the treatment period when discussions would be undertaken with parents about treatment withdrawal. Temperature fluctuations were no greater in the cooled group than in the control group, and there was no evidence that these fluctuations had any impact on safety and efficacy. Nor was there any evidence of therapy leading to a shift toward survival with severe neurological disability in a group of infants who previously would have died. In fact, the trend was toward a reduction in all three forms of disability measured by the assessment components of the primary efficacy outcome.

With regard to three anticipated consequences of hypothermia; namely, suppression of seizures which are unmasked during re-warming, prolongation of the QT interval, and inhibition of the metabolism and clearance of a range of anti-convulsant drugs, Dr. Wyatt sought to assure the Panel that they were of no major clinical significance. He believed that physicians should be informed of these possible effects of hypothermia. One patient had sclerema neonatorum, a rare condition which can be associated with serious underlying illness, or sometimes hypothermia; sclera neonatorum resolves if the underlying condition can be reversed. Another patient had an epidural hematoma, which appeared unrelated to the cooling therapy.

In summarizing the benefits of the Cool-Cap®, Dr. Wyatt noted that this is the first therapy which has been shown to improve outcome in encephalopathic infants, whose standard care currently consists of mechanical ventilation, anti-convulsants, and other supportive measures. Thus, although cooling is a major therapeutic intervention, when administered according to protocol, the benefits clearly outweigh the minimal risks.

Dr. Weiler returned to the podium to expand on the commercial Cool-Cap® enhancements that made the computer-based interface more user-friendly than the equipment used in the trial. He acknowledged the hard work of everyone involved with bringing the PMA to this point.

Panel Questions for the Sponsor

Panel members asked for additional information on inter-observer error and whether a core lab was used to determine consistency in reading aEEGs, details of the 18-month visit, late mortality as a surrogate for profound handicap, whether there was a difference in early withdrawal of care rates, the ability to measure brain temperature in neonates, whether mortality outcomes were tracked beyond six months, the coagulation profiles of the infants with bruising and scalp edema versus the epidural hematoma, whether the 0.042 p-value was computed by including the non-significant factors in the regression model, whether the Cox proportional hazard regression model represented a difference in time to mortality, for assurance that the assessment at 18 months was blinded, whether uncooled infants may have been survivors if they had been withdrawn from support, whether the data supported the hypothesis that applying the Cool-Cap® earlier in the six-hour window of opportunity led to better outcomes, and why rectal temperature and not nasopharyngeal temperature was used. The sponsor was given time over the lunch break to formulate responses to the longer questions.

FDA PRESENTATION

Kristen Bowsher, Ph.D., FDA's Lead Reviewer/Engineer, introduced the FDA review

team, reiterated the proposed indications for use and the regulatory history of the Cool-Cap® device. She described the device's cap, cooling unit, control unit, and temperature sensors and noted that an infant radiant warmer, although not part of the system, is necessary to maintain target rectal temperature. The user interface consists of a touch screen to display temperatures, an alarm to signal when the temperature range has been exceeded, and wizard screens to help with setup, re-warming and shutdown. The sponsor provided testing results that showed the device met IEC electrical safety and EMC standards, AAMI/ANSI/ISO biocompatibility standards, and ASTM packaging standards. Since updates were made to the user interface's software controls for the proposed commercial system as compared to the trial system, usability testing was performed to demonstrate that the changes did not adversely affect treatment use.

Susan K. McCune, M.D., M.A.Ed., a neonatologist in the Division of Pediatric Drug Development, presented the FDA's clinical review. By way of background she noted the prevalence rate of HIE, the rates of death and permanent neurological deficits caused by HIE, the pathophysiology of HIE, current supportive treatment of HIE, the presumed neuroprotective mechanism of action of hypothermia, and the window of opportunity for intervention with hypothermia. She described the study objectives and design, noting that the study was unmasked to avoid a potential increase in head temperature that a non-cooling cap might cause in control infants. With regard to the evaluation done at six-months, the protocol did not require that a systematic neurologic evaluation be performed. The protocol also did not include specific guidelines for referral for therapy and, although the number of patients referred for therapy at six month was recorded, no data were available on how many of the patients actually received therapy.

Inclusion criteria were that the infants had to be greater than or equal to 36 weeks gestation with one of the following: an Apgar score of less than five at ten minutes after birth, continued need for resuscitation at ten minutes after birth, acidosis within 60 minutes of birth, or a base deficit of more than or equal to 16 millimoles per liter in umbilical cord or any blood sample within 60 minutes of birth. Patients meeting those criteria were then assessed for neurologic abnormality, and then for abnormal background or seizures on amplitude integrated EEG. The majority of the entry criteria violations were related to randomization at more than 5.5 hours of age, less than 20 minutes of an aEEG recording, or a combination of the two. FDA granted approval for a continued access trial for up to 100 patients, and as of January 2005, 55 infants had been enrolled.

Dr. McCune then reiterated the safety data for the primary trial and the continued access trial, highlighting the areas where adverse events were increased for the cooled patients, while reminding the panel that no major adverse events were seen between the cooled and control groups. She discussed the issues surrounding the evaluation of the severity of encephalopathy using the Sarnat score as a measurement tool, seizure status, the inability to blind treatment, whether referral to therapy had an effect on the 18-month evaluation, and subpopulation analysis uncertainties. In terms of the primary effectiveness outcomes, the data showed a p-value of 0.10. However, after adjusting for baseline aEEG background, seizure status, Apgar score, birth weight, gender and age at randomization, statistical significance was demonstrated with a p-value of 0.042.

Jianxiong (George) Chu, Ph.D., FDA's statistician, focused on three areas in his presentation: the potential impact of missing data from the 16 lost-to-follow-up patients (LTFs) on the primary effectiveness endpoint, the six-month follow-up data regarding referral for

additional therapy, and the sponsor's original subgroup analysis.

The sponsor's logistic regression analysis for the treatment effect adjusting for aEEG background, aEEG-seizure status, and age (=0.053) excluded the 16 LTFs. To assess the impact of this exclusion, logistic regression analyses (intent-to-treat) adjusting for three additional covariates, i.e., gender, Apgar score, and birthweight, as discussed at the IDE stage, were conducted under several different scenarios. This sensitivity analysis showed a marginally significant treatment effect assuming the same outcome (success or failure) for the 16 LTFs or after multiple imputations for the missing primary outcomes. Under the best case scenario, assuming all successes for the 8 cooled group LTFs and all failures for the 8 control group LTFs, the treatment effect is statistically significant (p=0.002). However, under the worst cast scenario, assuming all failures for the 8 cooled group LTFs and all successes for the 8 control group LTFs, the treatment effect is not statistically significant (p=0.36).

Although a higher percentage of infants in the cooled group were referred for additional therapy at six months, it is difficult to assess the potential effect of any additional therapy because it is not known whether the therapy was actually received, or what the therapy was, or how frequently it was administered.

Finally, Dr. Chu asserted that no conclusions could be drawn from the sponsor's pooled subpopulation because the trial was not designed to demonstrate a statistically significant treatment effect within a particular subgroup, randomization was not stratified by sub grouping criteria, the overall treatment-by-subgroup interaction test was not statistically significant, and selection bias could be introduced by excluding a larger percentage of the most severely affected infants in the cooled group than in the control group.

Panel Questions for the FDA

Dr. Ellenberg asked about the post hoc addition of covariates used in the logistic regression analysis, which were not written in the protocol but were discussed with the FDA as being important to the analysis. Panel members also asked for more information about the aEEGs with regard to the lack of a core lab to verify results, the training involved in learning to read them, and their limited use as a tool to identify a subpopulation.

DELIBERATIONS

Reese H. Clark, M.D., opened the panel discussion with comments on the clinical diagnosis and incidence of neonatal encephalopathy and HIE in particular. He cautioned careful use of the term HIE, as it is a diagnosis that leads to many lawsuits in this country because it may imply some liability on the part of the health care providers. Since both the sponsor and the FDA reviewed the study design and outcomes, he went on to introduce the questions the FDA had posed and offered comments in the areas of defining a label that guides physicians to use the therapy in the safest way, feedback mechanisms that would trigger the device to shut off automatically if temperature bounds are exceeded, and whether a postmarketing study would be useful if the device is approved.

John Barks, M.D., a co-principal investigator from the University of Michigan, clarified for **Dr. Jayam-Trouth** that in his practice, lethargy, stupor or coma were factors in determining the entry criteria for altered state of consciousness and that patients needed to meet at least one

of the other inclusion criteria, such as abnormal reflexes or weak suck, as well. In response to a question about perhaps not indicating Cool-Cap® for use in patients with a Sarnat Stage 1 score, **Alistair Gunn, M.B.Ch.B., Ph.D.** of the Cool-Cap® trial's Scientific Advisory Committee clarified that too few patients were in that category to make such a recommendation meaningful. Dr. McCune added that it is not known why some infants classified as Sarnat Stage 3 (severe encephalopathy) do respond to cooling while some infants with severe aEEG background and seizure do not. She also corrected the base deficit on her inclusion criteria slide to be -16, not 16.

In response to Dr. Ellenberg's concern that surviving children doing better in the cooling arm were the driving force in creating the p-value of .042 in the combined endpoint of reduced mortality and developmental disability, Dr. Wyatt answered that both the trend to reduction in death and the trend to reduction in disability combined to reach statistical significance, so that, fortunately, the therapy does not simply convert babies who would have died of profound brain injury into survivors with severe disabilities.

Roberta Ballard, M.D., from the Cool-Cap® trial's Scientific Advisory Committee, then answered an earlier question about referrals to therapy at the six-month visit. Families were asked about whether or not they had been referred, but no referral was necessarily made at the time. Sites followed independent policies about whether they always referred babies with this history to therapy. As it turned out, cooled infants who were referred had better outcomes than controls who were referred, but conclusions cannot reliably be drawn from this fact. Drs. Ballard and Barks then discussed masking at the 18-month follow-up and how the results of the assessments were reviewed by blinded members of the sponsor's Scientific Advisory Committee. The fact that data were not gathered on those who had received therapy in the interim between the six- and 18-month visits was not seen as important by the sponsor because if therapy could change outcomes for severely disabled infants, it would be standard care.

Dr. Brott asked for details on how the Bayley, Gross Motor Function, and bilateral cortical visual examinations were administered and scored. **Dr. Hudak** asked about the hypothesis that parents whose infants were not on the Cool-Cap therapy were offered treatment withdrawal at an earlier time. The sponsor explained that the actual number of deaths at the end of the first week was the same in both cohorts, but that the time of death had been shifted for the cooled group compared with the control group. Additionally, the expectation that delaying withdrawal of care might result in more infants surviving with profound handicaps did not occur, so the effect of delaying withdrawal of care was deemed insignificant. Dr. Hudak wondered why the term "cerebral palsy" is avoided and why distributions weren't used in analyzing Bayley scores. The sponsor stated that since there were so few babies surviving in the moderate disability category, lumping them in the severe category did not change the outcome. By and large, the infants fit into two binary groups, normal or profoundly handicapped. **Dr. Doyle**, questioned why 18 months was picked as the second follow-up point and was informed that significant problems would be reliably detectable at this age, although 12 months or 24 months were also considered.

Dr. Coffey reminded the Panel that assessment of cortical blindness was well defined in the protocol but that no unilateral cortical visual deficits were detected at the 18-month follow-up and only 11 bilateral deficits were identified. A question about the durability of the 18-month outcomes prompted the sponsor to mention a potential follow-up study of these infants at age 7-10 years. There is a strong trend in the data toward protection with cooling of the brain's motor

functions, a dominant impairment of HIE. Although it seems unlikely that motor function would change over the years, one cannot reliably predict now whether certain learning disorders may emerge later.

Dr. Jensen found it curious that no one reviewed the aEEG data to ensure that correct categorization was made, but she was reminded that they were to be used to enrich the protocol, not as a primary outcome. Her questions regarding how staff were certified to read the tracings, why five tracings were unclassifiable, and whether the sponsor had any plans to retrospectively collect aEEGs to rule out inter-observer error were answered to her satisfaction, as was Dr. Jayam-Trouth's question about how to differentiate between aEEG levels. In Dr. Bark's experience, infants who were Sarnat Stage 2 who had a non-qualifying aEEG were excluded at the rate of two to three for every enrollee, but artifacts on the aEEGs may have confounded some entry decisions. When asked about whether any studies support cooling for longer than 72 hours, the sponsor answered that no studies have been done.

In the last round of questions, panel members asked about outcome consistency between large and small study sites and further clarification of the reason for performing the Fisher exact and the six-factor logistic regression. Visual Evoked Response was recommended as a better tool for assessing cortical visual deficit. Finally, the lack of imaging data on periventricular leukomalacia was noted, although this is a neuropathology predominantly seen in premature infants.

FDA QUESTIONS

1. There was a statistically significant difference between the cooled and control groups for minor cardiac arrhythmias and other adverse events. Additionally, there were more deaths in cooled infants than controls for 4 and 5 days after birth, and one patient from this investigation and two in the sponsor's continued access trial had the onset of seizures after warming. Please discuss the safety of the device in view of these findings.

The Panel was unanimous in its belief that these were not significant safety concerns, given the anticipated nature of the adverse events and given how sick the patients were. One Panel member thought the issue of withdrawal of care should be addressed in the labeling.

2. Logistic regression analysis adjusting for baseline aEEG background, seizure status, Apgar score, birth weight, gender, and age at randomization indicated a treatment effect of statistical significance. Additionally, the sponsor performed an analysis in which they excluded patients with severe aEEG backgrounds and seizures. Based on the study results, please discuss whether use of the device should be limited to a particular subset of the HIE population (e.g., gestational age, weight, size, aEEG, etc.).

The Panel generally agreed that there was no evidence in favor of placing further limitations on the target population and that the labeling should reflect the patients who were actually studied. Several Panel members expressed concern about the use of aEEG and one suggested Sarnat scores as an alternative. The statistician was not in favor of breaking out the subgroup analysis on the labeling.

3. Please discuss any potential safety and/or effectiveness concerns raised by the difficulty in maintaining the target temperature range specified in the study protocol and whether

the instructions for use should be modified to include more detailed guidance for maintaining proper temperature.

Panel members had no strong concerns regarding how temperature fluctuations might affect the system's safety and effectiveness. Some panel members expressed a desire to improve the temperature regulation system with addition of a closed-loop feature. They were reminded that other variables independent of the Cool-Cap® system and the infant radiant warmer, such as phenobarbital administration and subclinical seizures, impact thermoregulation.

4. The sponsor has provided draft labeling for the device which includes the indications for use, contraindications, warnings, precautions, and instructions for using the device. Please discuss whether the device should be further limited in its use (e.g., time of cooling start, duration of cooling, degree of cooling, etc.) and whether any additional information should be included in the labeling.

The Panel believed strongly that the labeling should reflect the indications and contraindications as they were applied in the study, with one Panel member advocating a mention of the lack of data to substantiate the device's benefit beyond 72 hours of cooling. Another urged inclusion of a notice reminding users that "every minute counts," but it was suggested that this could be emphasized in training courses.

5. Please discuss whether the data in the PMA provide a reasonable assurance of safety as defined in 21 CFR 860.7(d)(1).

The Panel unanimously agreed that the data provided a reasonable assurance of safety.

6. Please discuss whether the data in the PMA provide a reasonable assurance of effectiveness as defined in 21 CFR 860.7(e)(1).

The Chairperson summarized the Panel's opinion as agreeing that clinical significance had been demonstrated, although Drs. Jayam-Trouth and Brott used the term "clinically promising." Dr. Clark said the trial as designed did not show efficacy, but that the subgroup analysis was promising, to which Dr. Jensen agreed, although he thought reasonable assurance was demonstrated. Drs. Nelson, Coffey, Doyle, Hudak and Haines were assured there was a treatment effect to meet the criterion of clinical significance, as opposed to statistical significance, while Dr. Ellenberg believed there had not been appropriate evidence of efficacy.

7. If you believe that the data in the PMA demonstrate a reasonable assurance of safety and effectiveness, but think there are specific focused questions regarding this device that still remain and can be addressed in a post-approval study, please identify those questions.

Dr. Jensen would like to see the question of appropriate inclusion/exclusion criteria answered if it is decided to use Sarnat scores instead of aEEGs, as specified in the trial. Dr. Hudak suggested a randomized, controlled trial of babies who are Sarnat 2 or 3 who have normal aEEG findings and no seizures, but Dr. Nelson cautioned that the real-world pressure to use this therapy once approved may make such a study unfeasible. Dr. Brott spoke in favor of the proposed study of these patients at seven to ten years of age to test the durability of the 18-month outcomes. He speculated that modern imaging techniques could potentially replace the five-page questionnaire. Dr. Clark suggested setting up a registry, continuing to follow patients in the continued access study, and better defining who might and might not benefit from this

therapy. Dr. Jayam-Trouth agreed that further identification of what subpopulations would most benefit would prevent every neonatal infant with an Apgar of 6 from ending up with a Cool-Cap®. Dr. Coffey was not in favor of post-approval trials since the risk of failure of this therapy is quite different from the actual risk to the patient.

OPEN PUBLIC HEARING

No comments were made.

VOTE

Ms. Scudiero read the voting options. The panel voted five to one, with one abstention, to recommend approval of the PMA with the following conditions:

1. That a registry of all patients treated with the Cool-Cap® device be maintained.
2. That there be a formal training program, including a didactic component, a technical equipment management component, and a certification component, for all users of the device.
3. That the labeling reflect the inclusion and exclusion criteria of the clinical trial.

POLL

Panel members voting to recommend approval of the PMA with conditions believed that the safety risks were minimal and that the treatment effect was sufficiently compelling to justify its use in infants at risk for HIE for whom there are few other treatments apart from supportive care.

Panel members voting no and abstaining were not convinced that the primary efficacy outcome was met. There was also a concern about bias with regard to the 18-month assessments.

ADJOURNMENT

On behalf of the FDA, Dr. Provost thanked the panel and the members of the public who testified, and Dr. Haines adjourned the meeting at 4:31 p.m.

I certify that I attended this meeting of the
Neurological Devices Advisory Panel
on June 17, 2005, and that these minutes accurately
reflect what transpired.

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Janet L. Scudiero, M.S.
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

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Stephen J. Haines, M.D.
Chairperson

07/18/05 JLS first edit: minor edits accepted, others left for review team comment

08/11/05 JLS inserted S McCune's and S Buckman's changes (most were minor one word changes); they had one question on p. 6.

G Chu's changes included one major paragraph rewrite that was inserted as tracked changes and some smaller changes (single word or a few word phrases); his minor changes (1-2 words were accepted. His comments probably could be shortened.

08/12/05 JLS Incorporated 3 minor changes from S McCune and G Chu
08/23/05 JLS accepted M Provosts editorial comments; referred her comment questions to KXB and SMcM
09/12/05 JLS Revised per S McC's comments on Miriam's comments; will send to S McC & KXB one more time.
09/14/05 S McC agreed with last edits; JLS accepted changes